EXHIBIT A

Paper No. 45

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MICHAEL S. NEUBERGER and TERRENCE H. RABBITTS

Appeal No. 1999-1355
Application No. 08/469,786[1]

ON BRIEF

Before WINTERS, WILLIAM F. SMITH and SCHEINER, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 35 through 47, all the claims remaining in the application.

[1] Application for patent filed June 6, 1995. According to appellants, this application is a continuation of application no. 08/185,440, filed January 24, 1994, now abandoned, which is a continuation of application no. 07/994,078, filed December 17, 1992, now abandoned, which is a continuation of application no. 07/489,207, filed March 6, 1990, now abandoned, which is a continuation of application no. 06/865,816, filed May 2, 1986, now abandoned.

Claims 35 and 42 are representative of the subject matter on appeal and read as follows:

35. A chimeric antibody comprising an Ig moiety having antigen binding activity and a non-Ig protein moiety comprising a protein having biological activity or a biologically active portion thereof, wherein said non-Ig protein moiety is carboxy terminal to said Ig moiety, said chimeric antibody having said antigen binding activity and said biological activity.

42. A process for the production of a chimeric antibody comprising an Ig moiety having antigen binding activity and an non-Ig protein moiety comprising a protein having biological activity or a biologically active portion thereof, wherein said non-Ig protein moiety is carboxy terminal to said Ig moiety, said chimeric antibody having said antigen binding activity and said biological activity, said process comprising;

i) preparing a replicable expression vector comprising a promoter operably linked to a DNA sequence comprising a first part encoding at least a variable region of an antigen-binding Ig polypeptide chain and a second part 3' of said first part encoding a biologically functional non-Ig protein, or a biologically active portion thereof, wherein said first and second parts are combined such that expression results in a product possessing said variable region capable of binding antigen and said non-Ig protein capable of exhibiting its biological function as expressed;

ii) transforming an immortalized mammalian cell line that secretes an Ig polypeptide chain complementary to the variable region encoded in said DNA sequence with said vector; and

iii) culturing the transformed cell line under conditions such that said DNA sequence is expressed and such that assembly of said chimeric antibody is effected so that said variable region is immunologically active and said non-Ig protein moiety is biologically functional.

The references relied on by the examiner are:

Hopp et al. (Hopp)	4,703,004	Oct. 27, 1987
Cabilly et al. (Cabilly)	4,816,567	Mar. 28, 1989

Lehninger, in Biochemistry, Worth Publishers, Inc., New York, NY, page 125 (1970)

Neuberger, "Expression and Regulation of Immunoglobulin Heavy Chain Gene Transfected into Lymphoid Cells," The EMBO Journal, Vol. 2, No. 8, pp. 1373-1378 (1983)

Claims 35-47 stand rejected under the first paragraph of 35 U.S.C. § 112 as not enabled throughout their scope by the specification. In addition, claims 35-41 stand rejected under 35 U.S.C. § 103 as unpatentable over Neuberger, Cabilly and Hopp, while claims 42-47 stand rejected under 35 U.S.C. § 103 as unpatentable over Neuberger and Hopp.

We reverse all three of the rejections.

DISCUSSION

Enablement

In its broadest aspect, the claimed invention is directed to a chimeric protein (and methods of making it) comprising an immunoglobulin moiety "having antigen binding activity" and a non-immunoglobulin protein moiety "having a biological activity," wherein the non-immunoglobulin moiety is "carboxy terminal to" the immunoglobulin moiety, and the chimeric protein "[has] said antigen binding activity and said biological activity." Claim 1. According to the examiner, however, the specification "is enabling only for claims limited to chimeric antibodies which comprise a biologically functional non-Ig protein for which working examples are disclosed in the specification." Answer, page 6.

At the outset, we note that the examiner has applied this rejection to all of the claims on appeal, even claims 38-41, which specify that the non-Ig portion of the hybrid protein is RNase, the Klenow fragment of DNA polymerase I, ricin or c-myc. Inasmuch as these claims correspond to the working examples, and the examiner has conceded that the specification is enabling for "chimeric antibodies which comprise a biologically functional non-Ig protein for which working examples are disclosed in the specification," the continued rejection of claims 38-41 on the ground of lack of enablement is illogical

on its face. That being said, for reasons which follow, we find that the rejection is without merit for the broader claims as well.

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'" Id. at 1561, 27 USPQ2d at 1513. "That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these considerations are the so-called Wands factors, including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." Id.

The examiner indirectly touches on a few of the Wands factors (Answer, pages 7 and 8), arguing that

> [D]isclosure of three functional chimeric antibodies is insufficient evidence to support the present claims as to all chimeric antibodies prepared from all non-Ig proteins as being functional.
>
> The specification examples, while differing structurally and functionally, are not representative of all classes of non-Ig protein moieties nor that when coupled to an Ig, that the chimeric protein would have retained the properties of both parts of the chimeric protein . . .
>
> [T]he biological activity [and] function of a protein are greatly dependent upon its three-dimensional configuration . . . and [ ] even minor changes in the sequence of a protein may adversely affect its ability to fold properly. Changes in DNA sequence may alter the ability of a transfected cell to express, secrete and properly assemble the protein. The present application disclosure does not disclose nor guide one skilled in the art . . . as to the parameters that affect and/or effect the predictability of the retention of biological activity and function for both the non-Ig segment and the Ig segment of the chimeric protein. The indicia of certainty is not apparent in the application as filed. Thus, one of skill in the art . . . would not have been able to predict with certainty or even a priori that biologically active and functional chimeric antibodies would have been produced from all expression constructs.

This argument is not persuasive for several reasons. To the extent that the examiner requires "certainty" to demonstrate enablement, we note that no authority has been cited in support of this requirement. On the contrary, a requirement for certainty would be incompatible with any amount of experimentation and therefore incompatible with the standard of enablement discussed above. Nor is it the function of the claims to specifically exclude possibly inoperative embodiments - only if the number of inoperative embodiments becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, might the claims be invalid. See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984).

We accept, for the sake of argument, that many chimeric proteins will not fold properly, will not function properly, and may not be secreted properly, and that a certain amount of experimentation would be required to identify those that will. But quantity of experimentation is only one factor in determining whether the experimentation is undue. Others factors are the amount of direction or guidance presented, and the presence or absence of working examples. Here, the fact that the specification demonstrates the successful production of several different hybrid proteins comprising antibodies joined to members of several different protein classes (Specification, Examples 1-5, pages 12-28) weighs heavily in favor of a finding of enablement for claims broader than the working examples. The examiner's summary dismissal of the examples as "not representative of all classes of non-Ig protein moieties" is not evidence, and does not provide a reasonable basis to question the adequacy of the disclosure provided for the claimed invention.

In our judgment, the reasons cited in support of the examiner's rejection are insufficient to support the examiner's conclusion that "the present specification does not enable the scope of the claims" (Answer, page 10).

Accordingly, the rejection of claims 35-47 under the first paragraph of 35 U.S.C. § 112 is reversed.

Obviousness

All of the claims on appeal stand rejected under 35 U.S.C. § 103. With respect to claims 35-41, the examiner relies on Neuberger, Cabilly and Hopp as evidence of obviousness; with respect to claims 42-47, the examiner relies on Neuberger and Hopp.

Neuberger and Cabilly are cited principally to establish that recombinant antibodies were known in the art at the time of the invention. Neither reference describes antibody-non-antibody hybrid proteins, and the examiner relies on Hopp as evidence that "the production of hybrid proteins was known in the art." Answer, page 11. According to the examiner, Hopp "teach[es] the synthesis of hybrid proteins including antibodies . . . and for example, toxic proteins . . . by recombinant DNA techniques" and "also disclose[s] vectors encoding identification peptides and cleavable linker sequences that facilitate[ ] purification of desired proteins." Id.[2]

In the examiner's opinion, it would have been obvious "to have modified the teachings of either [Neuberger or Cabilly] by transfecting cells with vectors containing hybrid immunoglobulin genes as taught by [Hopp] in order to obtain bifunctional chimeric antibodies containing as part of that antibody, an identification peptide where any peptide protein is an identification peptide." Answer, page 11.

"[T]he examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met does the burden of coming forward with

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[2] The examiner's wording here is somewhat misleading - Hopp does not disclose antibody-toxin hybrids, rather, the reference describes hybrids between "selected proteins" and "identification peptides." The selected protein portion of the hybrid may be an antibody or a toxin, but the reference does not describe an antibody connected to a toxin - instead, each is connected to an identification peptide. See, e.g., column 5, lines 9-15 and column 6, lines 55-58.

evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of the invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." In re Dembiczac, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

On this record, we find that the examiner's initial burden of presenting a prima facie case of obviousness has not been met. Hopp describes "[a] hybrid molecule composed of a selected . . . protein and an identification or marker peptide," wherein "[t]he identification peptide ideally includes two primary components: a highly antigenic N-terminal portion; and, a linking portion to connect the identification peptide to the protein . . . [which] is characterized by being cleavable at a specific amino acid residue adjacent the protein molecule by use of a sequence specific proteolytic agent." Column 2, lines 53-63. The "selected protein" portion of Hopp's hybrid "may be . . . substantially any . . . protein that can be expressed by a vector in a transformed host cell," including an enzyme, a storage protein, a transport protein, an antibody, a hormone, a toxin, etc. Column 6, line 55 to column 7, line 25.

Whether or not Hopp's hybrid molecule can be considered to be a hybrid between a biologically functional non-immunoglobulin protein and an immunoglobulin is an open question, and one we need not answer here. It is enough to note that the examiner has failed to come to grips with fact that all of the claims on appeal require that the non-immunoglobulin protein moiety of the hybrid protein be connected to the

Hopp explicitly states that "[t]he identification peptide is . . . a linear sequence of amino acids bonded to the N-terminus of the protein of interest" (emphasis added) and "is composed of two basic portions: an antigenic N-terminus or 'head' portion; and a linking or 'tail' portion to link the identification peptide to the selected protein molecule." Column 5, lines 9-15. The linking portion of the identification peptide is "composed of a sequence of amino acids ending with either Lys, Arg, Met or Asn, so that "a proteolytic enzyme that cleaves after the Arg or Lys residue can be used . . . or an appropriate chemical agent that cleaves after [Met or Asn] may be employed to sever the identification peptide from the protein molecule" (Column 6, lines 4-12), "ideally at the residue adjacent the N-terminus of the protein molecule" (Column 5, lines 51-55). "By this particular construction of the identification peptide, the hybrid . . . molecules expressed by the transformed host cells can be isolated by affinity chromatography techniques . . . [and] the identification peptide [can be] cleaved from the protein molecule . . . releasing the desired, highly purified protein." Column 2, line 63 to column 3, line 7. Clearly, the orientation of the two moieties of the protein-peptide hybrid is dictated by Hopp's ultimate goal: isolation and purification of the selected protein.

In responding to appellants' comments on this issue, the examiner argues (Answer, page 24) that

> One of ordinary skill in the art would have known that the genetic material encoding the immunoglobulin constant region is 3' to the genetic material encoding the variable region of an antibody chain . . . [and] would have constructed the gene of the Ig-protein chimera analogous to the structure of the Ig gene constructs containing the variable and constant region gene segments . . . since anyone of ordinary skill in the art would also have known that a functional antibody has a variable region domain in the protein that is antigen specific and [Hopp] as well as each of [Neuberger]

> . . . It is also known in the art that linkage of the polynucleic acid segment encoding the non-Ig protein moiety to the 5' end of the genetic construct encoding the variable segment . . . would have been expected to interfere with the antigen binding site . . .

The examiner concludes that "no one of ordinary skill in the art having the references would have put the identification peptide where appellant asserts especially where the combined references are directed to producing and disclosure of bifunctional antibodies." Answer, page 24. This presupposes that one would have had a reason to modify Hopp (or Neuberger or Cabilly) in the first place - something the examiner has not established.

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." In re Fritch, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992), citing In re Gorman, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). The examiner may establish a case of prima facie obviousness based on a combination of references "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." Id., 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

On this record, the only reason or suggestion to combine the references in the manner claimed comes from appellant's specification. Accordingly, the rejection of claims 35-47 under 35 U.S.C. § 103 is reversed.

CONCLUSION

On consideration of the record, we have reversed the rejection of the claims under the first paragraph of 35 U.S.C. § 112, as well as the rejections of the claims under 35 U.S.C. § 103.

REVERSED

Sherman D. Winters
Administrative Patent Judge

William F. Smith
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

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